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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

DECLARATION OF DAVID H. PERSING, Ph.D., M.D. IN SUPPORT OF VYSIS' OPPOSITION TO GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT OF NONINFRINGEMENT UNDER THE DOCTRINE OF EQUIVALENTS

Date: November 13, 2001
Time: 10:30 a.m.
Place: Courtroom 1

FILED BY FAX

I, Dr. David H. Persing, Ph.D., M.D., declare as follows:

1. I have personal knowledge of the facts set forth herein, and if called as a witness would testify to the truth thereof.

2. I am presently Vice President, Molecular Biology, at Corixa Corporation, and Medical Director, Infectious Disease Research Institute, both in Seattle, Washington. I received a Ph.D. (Department of Biochemistry and Biophysics) and an M.D. (School of Medicine) from the University of California, San Francisco in 1988. My Ph.D. work was performed in the laboratory of Nobel laureate Harold Varmus. I was a Resident and Research Fellow at the Yale School of Medicine from 1988-1990. I was employed by the Mayo Clinic, Rochester, Minnesota from 1990 to 1999. My work has been primarily directed to the study of infectious diseases, including study of the application of nucleic acid hybridization assays in medical diagnostics. I was director from 1993 to 1999 of the Molecular Microbiology Lab of the Mayo Clinic, which was one of the premier centers for the diagnosis of infectious diseases by molecular methods. There, I pioneered techniques for pathogen discovery and contamination control, and discovered several new pathogens. I am a member of three Scientific Advisory Boards, including the Scientific Advisory Board of Vysis, Inc., and am an Editor-in-Chief of the reference text Diagnostic Molecular Microbiology PRINCIPLES AND APPLICATIONS. A list of my patents and scientific publications is included in my curriculum vitae attached as Exhibit A.

3. I have extensive experience in the fields of nucleic acid hybridization and amplification. I have been familiar with and been a practitioner of nucleic acid hybridization assays and various amplification techniques used with nucleic acid hybridization assays since about 1985. As indicated in Exhibit A, I have a number of scientific publications relating to these techniques.

4. I have been retained as an expert by Vysis in this lawsuit. In that regard, I have reviewed the claims, specification, and pertinent prosecution history of U.S. Patent No. 5,750,338 ("the '338 patent"). I have also reviewed material produced by Gen-Probe that describes the target capture, amplification, and detection processes used in Gen-Probe's HIV/HCV test.

5. After comparing Gen-Probe's HIV/HCV test with the claims of the '338 patent, it is my opinion that Gen-Probe's TMA technique of amplifying target nucleic acids is not substantially different from the methods of amplification disclosed and claimed in the '338 patent, even if the '338 patent claims are limited to non-specific amplification techniques.

6. At the outset, it is important to note that all nucleic acid amplification techniques have some element of non-specificity. Thus, even so-called specific amplification protocols, such as polymerase chain reaction ("PCR") amplification and Gen-Probe's TMA amplification are non-specific to varying degrees. The degree of nonspecificity of an amplification protocol depends on the conditions of amplification and the intrinsic properties of the protocol. In general, TMA is less target-specific than PCR. That is one reason why Gen-Probe uses target capture in its HIV/HCV assay – to purify the target prior to amplification, thus minimizing amplification of non-target sequences.

7. The purpose of Gen-Probe's TMA technique is to enable the production of a multitude of target polynucleotides from a sample that may initially contain only very few target polynucleotides. That process permits detection of the presence of a target polynucleotide that may otherwise go undetected as a result of its low concentration in a clinical sample.

8. The TMA technique involves creation of a double-stranded DNA molecule from a single-stranded target polynucleotide. The TMA technique, across several amplification cycles, then uses RNA polymerase to create multiple RNA molecules from that double-stranded DNA. Those RNA molecules are then detected by contacting them with a complementary labeled DNA probe.

9. The amplification techniques disclosed and claimed in the '338 patent perform in substantially the same way. For example, Example 5 of the '338 patent teaches the creation of a double-stranded DNA molecule from a single-stranded target polynucleotide. Example 5 then teaches the use of RNA polymerase to create multiple RNA molecules from that double-stranded DNA. As in Gen-Probe's TMA process, those RNA molecules are detected by contacting them with a complementary labeled DNA probe.

10. The differences between Gen-Probe's TMA technique and the techniques disclosed and claimed in the '338 patent are insignificant from a practical perspective. For example, the target

polynucleotide of the TMA process may be RNA or DNA. Indeed, Gen-Probe touts its TMA process as able to use either RNA or DNA as a target. (See Hill, "Gen-Probe Transcription-Mediated Amplification: System Principles" (Exhibit A).) Example 5 of the '338 patent uses single-stranded DNA as a target. From a practical standpoint, there is no substantial difference between these targets. Both are used as templates for the creation of double-stranded DNA, which is then used in both processes to create RNA polynucleotides. Another difference between Gen-Probe's TMA process and the amplification process disclosed in Example 5 of the '338 patent is the use of different primers. Again, this is not a substantial difference.

11. Gen-Probe's TMA process uses "specific" primers – that is, primers that have a nucleotide sequence that has been pre-selected to bind with the target polynucleotide at a predetermined sequence. Two "specific" primers are used in the TMA process. These primers are used as a "starting point" for the enzyme that creates the double-stranded DNA molecule.

12. Example 5 of the '338 patent discusses the use of "random" primers. These primers act in the same way as the primers of the TMA technique – they bind to the target polynucleotide and act as the "starting point" for the enzyme that creates the double-stranded DNA molecule.

13. Although most "random" primers do not bind to a predetermined sequence of the target polynucleotide, this difference is inconsequential since at least some of the random primers bind to the target in a sequence-specific fashion, thus initiating nucleic acid synthesis. As long as a double-stranded DNA molecule is created, the particular location of the target polynucleotide to which the primers bind is not important. Because the target capture step disclosed and claimed in the '338 patent acts to eliminate polynucleotides other than the target, "random" primers will bind only to the target polynucleotide.

14. Accordingly, the same result – creation of double-stranded DNA – is reached whether one uses "specific" primers or "random" primers. Indeed, one could use the "specific" primers of Gen-Probe's TMA process in place of the "random" primers of Example 5 and achieve exactly the same result. The amplification techniques of the '338 patent will work regardless of whether the primers are "specific" or "random."

15. One of the "specific" primers used in Gen-Probe's TMA technique also contains a "promoter" sequence. This "promoter" sequence is recognized by the RNA polymerase enzyme, which creates RNA molecules from the double-stranded DNA. The "promoter" sequence tells the RNA polymerase where to begin transcription of the RNA molecules.

16. The amplification process of Example 5 also uses an RNA polymerase, but does not require a "promoter" sequence to begin work. The RNA polymerase of Example 5 has been modified by removing the "sigma subunit." This modified RNA polymerase allows RNA transcription to begin from any point along the double-stranded DNA molecule. Again, however, the result of the two processes is the same – RNA molecules are transcribed from the double-stranded DNA molecules.

October 29, 2001

David H. Persing, Ph.D., M.D.

EXHIBITS

Declaration of David H. Persing, Ph.D., M.D. in Support of Vysis' Opposition to Gen-Probe Incorporated's Motion for Partial Summary Judgment of Noninfringement under the Doctrine of Equivalents